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July 19, 2006

Steve Johnson, Administrator  
US Environmental Protection Agency  
Ariel Rios Building  
Room 3000, #1101-A  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

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Subject: Comments on the HPV test plan for the chemical Cyclohexanone oxime

Dear Administrator Johnson:

The following are comments on the test plan for the chemical cyclohexanone oxime (**CAS# 100-64-1**) for the HPV program, submitted by the DSM Chemicals North America, Inc. (DSM). These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

Although several HPV endpoints in this test plan are not fulfilled, DSM has provided extensive information on the closed-system intermediate (**CSI**) status of cyclohexanone oxime, justifying an exemption from ecotoxicity and environmental fate testing, as well as mammalian reproductive testing. However, DSM proposes a "developmental toxicity study" by oral route, "following OECD guidelines," as CSI chemicals are not exempted from developmental toxicity testing. It is unclear which OECD guideline DSM plans to follow, which is serious cause for concern, since a "developmental toxicity study," OECD TG 414, uses hundreds more animals than a "combined reproductive/developmental toxicity study," OECD TG 421 (1300 and 675 animals, respectively). Even more disconcerting is a sentence on page 3 of the test plan that seems to imply that the study has a protocol approved and a scheduled initiation at a laboratory, with the animals and test substance already bought. DSM states: "An appropriate study to meet the HPV requirement...will be conducted **starting** in the 3<sup>rd</sup> or 4<sup>th</sup> quarter of 2006 and take less than a year to complete." We certainly hope that DSM plans to consider EPA and public comments before committing to fund or conduct such a study; to fail to do so would be in violation of the HPV Challenge Program.

Additionally, given metabolism and distribution data from a reference cited in the test plan (**1**), it may be possible to eliminate the developmental toxicity "data gap" in this test plan. It appears that cyclohexanone oxime undergoes a Phase I hydrolysis reaction to cyclohexanone, and further to cyclohexanol, which is then eliminated **after** Phase II glucuronidation. Further, there is a wealth of information on the developmental toxicity potential of cyclohexanone and cyclohexanol (2-9). It is recommended that DSM consider using the information from the cyclohexanone oxime metabolites to fulfill the developmental toxicity endpoint for cyclohexanone oxime. It is imperative that DSM investigate this possibility more fully before committing to a "developmental toxicity study," as stated in their test plan.

This EPA-accepted strategy has been used by other companies to fulfill HPV test plan requirements, and we would be more than willing to discuss the particulars with DSM at any time.

Thank you for your attention to this issue. We can be reached at 202-686-2210 ext. 335 or via e-mail at [kstoick@pcrm.org](mailto:kstoick@pcrm.org) with any questions or concerns.

Sincerely,

Kristie **Stoick**, MPH  
Research Analyst

Chad B. Sandusky, PhD  
Director of Research

1. **Parmar**, D and Burka LT. Metabolism and disposition of cyclohexanone oxime in male F-344 rats. **Drug Metab Dispos** **19(6):1101-7 (1991)**.
2. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes **I, II, III**. Cincinnati, OH: ACGIH, **1991**., p. 359.
3. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes **I, II, III**. Cincinnati, OH: ACGIH, **1991**., p. 357
4. **Bio/dynamics** Inc; An Inhalation Teratogenicity Study in the Mouse with Cyclohexanone, **(1984)**, EPA Document No **40-8466096**, Fiche No **OTS0507478**.
5. **Bio/dynamics** Inc; An Inhalation Teratology Study in Rats with Cyclohexanone, Final Report, **(1984)**, EPA Document No 40-8466096, Fiche No **OTS0507478**.
6. **IARC**. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, **1972-PRESENT**. (Multivolume work)., p. V47 163 **(1989)**.
7. Seidenberg JM and Becker RA. Teratog Carconig Mutagen **7:17-28 (1987)**.
8. Seidenberg JM, Anderson DG and Becker RA. Teratog Carconig Mutagen **6:361-374 (1986)**.
9. Shane BS. Humane reproductive hazards: evaluation and chemical etiology. *Environ Sci Technol* **23(10): 1187-95 (1989)**.